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Atty Docket No. 20695C-002200US

PTO FAX NO.: 1-571-273-8300

ATTENTION: Examiner Stacy Brown Chen

Group Art Unit 1648

OFFICIAL COMMUNICATION

FOR THE PERSONAL ATTENTION OF

EXAMINER Stacy Brown Chen

CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that the following documents in re Application of , Application No. 10/006,671, filed December 10, 2001 for ENVELOPED VIRUS VACCINE AND METHOD FOR PRODUCTION are being facsimile transmitted to the Patent and Trademark Office on the date shown below.

Documents Attached

1. Executed Declaration of Kistner and Reiter

Number of pages being transmitted, including this page: 5

Dated: April 13, 2006

Stephanie J. Whitehurst

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TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, CA 94111-3834
Telephone: 415-576-0200
Fax: 415-576-0300
0106

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kistner, et al.

Application No.: 10/006,671

Filed: December 10, 2001

For: ENVELOPED VIRUS VACCINE AND METHOD OF PRODUCTION

Customer No.: 20350

Declaration of Kistner and Reiter

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

We, Otfried Kistner and Manfred Reiter, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both, under 18 U.S.C. § 1001, and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of our own knowledge are true and statements made on information or beliefs are believed to be true.

2. I, Otfried Kistner, am currently a Scientist and Senior Director of Virology and Viral Vaccines at Baxter BioScience, in Orth/Donau, Austria. I have worked in the field of Virology and Vaccine development for 22 years. I have a Ph.D. degree in virology from the Justus –Liebig University of Giessen. A copy of my *Curriculum Vitae* is attached as Exhibit A. I, Manfred Reiter, am currently a Scientist and Director of Upstream Process Development at Baxter BioScience, in Orth/Donau, Austria. I have worked in the field of process development for 20 years. I have a Ph.D. degree in Biotechnology from the

University of Agriculture and Forestry, Vienna . A copy of my *Curriculum Vitae* is attached as Exhibit B. We are the joint inventors of the above-referenced application, filed on December 10, 2001.

3. We have reviewed the Office Action mailed on October 12, 2005 in connection with the above-referenced application. We understand that the Examiner has rejected claims 1, 2, 4, 7-9, 11, 14-17 and 27-31 as being allegedly obvious over U.S. Patent No. 5,789,245, Dubensky *et al.* (herein "Dubensky"). In particular, we understand that the Examiner asserts that "[H]ad one of ordinary skill performed Dubensky's method with RRV, the virus intermediate would have necessarily been about 97% pure," as achieved in our methods. This declaration is provided to show that, in fact, Dubensky's method cannot produce virus of the purity achieved by our method.

4. We have performed an experiment in the laboratory wherein we carried out Dubensky's method next to our own method in order to obtain RRV intermediate so that we could test and compare its purity. A VERO cell culture was infected with RRV, incubated and propagated in a bioreactor. More specifically, cells of a working cell bank were expanded in T-flasks and roller bottles with a split ratio of 1:6. Propagation of the cells was performed in a stirred tank bioreactor using CYTODEX3 microcarrier as attachment substrate. The cells were grown at 37°C. The culture conditions of oxygen saturation 20% +/- 10% and pH 7.25 +/- 0.35 were kept constant during virus propagation. A serum free VERO cell culture was infected with RRV at a multiplicity of infection of 0.001. After an incubation time of three days (66 hrs) at 37°C the virus was harvested from the bioreactor.

5. First, we followed Dubensky's teachings and passed the harvested virus through a 0.8/0.65 micron filter in order to clarify the crude RRV according to Dubensky's method (see column 120 in U.S. Patent No. 5,789,245). Second, we followed the teachings of the specification and passed the virus harvest (from the same bioreactor), after separation at ~9000g through a 1.2 micron filter and then through a 0.45 micron filter and finally through a 0.22 micron filter in order to clarify the crude RRV according to our own

method (see page 12, paragraph 049 of the specification). We then assessed the purity of each virus intermediate through Vero-DNA, protein and TCID50 analysis

6. The results showed that the RRV intermediate obtained with our method has a DNA content of 11.8 ng (0.45µ filter) and 11.9 ng (0.22m filter) per 10^7 TCID50 while the RRV intermediate obtained with Dubensky's method has a DNA content of 95.7 ng DNA per 10^7 TCID50. In addition, we have compared the purity of the virus intermediates (obtained with each method) on a DNA to total protein basis and established that Dubensky's method would only lead to an intermediate virus product of 1.62ng DNA per µg protein. In comparison, our method leads to substantially higher purity of the intermediate with a DNA content of 0.23 ng per µg of protein (1.2/45µ filtration) and a DNA content of 0.08 ng per µg protein for the 1.2/0.45µ/0.22µ filtration. Both size exclusions, 0,2 and 0.45 were chosen according to the published pore size range of 0.1-0.5 micron. In addition, we have filtered the 0.8/0.65 micron filtrate (intermediate according to Dubensky's method) with a 0.22micron filter. With this additional filtration step according to our method a significant decrease in DNA content to 63.4 ng/10^7 TCID50and an improved DNA/protein ratio 0.73ng per µg of protein could be achieved. For all experiments identical starting material with a TCID50 of 4.91 x 10^7 was used. The results are summarized in the tables below:

THE CLAIMED METHOD		
	DNA/Virus Titer [ngDNA/10^7($TCID_{50}$/ml)]	DNA/Protein [ngDNA/μgProtein]
Filtration: 1.2 μm/0.45 μm	11.8	0.23
Filtration: 1.2 μm/0.45/0.2 μm	11.9	0.08

DUBENSKY'S METHOD		
	DNA/Virus Titer [ngDNA/10^7($TCID_{50}$/ml)]	DNA/Protein [ngDNA/μgProtein]
Filtration: 0.8 μm/0.65 μm	95.7	1.62
Filtration: 0.8 μm/0.65 μm/0.2μm	63.4	0.73

13 April 2006 — Date

Otfried Kistner, Ph.D.

13 April 2006 — Date

Manfred Reiter, Ph.D.

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